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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/833,203	04/12/2001	Maurice Zauderer	1821.0020001	1700

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EXAMINER
VANDERVEGT, FRANCOIS P

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 08/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/833,203	ZAUDERER ET AL.	
	Examiner	Art Unit	
	F. Pierre VanderVegt	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 May 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-33,35-37,39 and 121-130* is/are pending in the application.

4a) Of the above claim(s) *28-30,32,33,35,121-123,125-127 and 129* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27,31,36,39,120,124,128 and 130* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This application claims the benefit of the filing date of provisional application 60/196,472.

Claims 1-26, 34, 38 and 40-119 have been canceled.

Claims 27-33, 35-37, 39 and 120-130 are currently pending.

Applicant is reminded of the requirement to affix the proper status identifiers to the claims in the complete listing of the claims.

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 24, 2006 has been entered.

Election/Restrictions

2. In accordance with the original Restriction requirement and the election of September 3, 2002, **claims 28-30, 32, 33, 35, 37, 121-123, 125-127 and 129 stand as withdrawn** from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the response filed September 3, 2002.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 27, 31, 36, 39, 120, 124, 128 and 130 stand rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/64464 (Savage, PM; AL3 on form PTO-1449 filed March 19, 2003) in view of Cormier et al. (Int. J. Cancer 1998 75:517-524; U1 on form PTO-892), Schnell et al. (J. Immunol. 2000 164:1243-1250; V1 on form PTO-892) and Zarour et al. (AR23 on form PTO-1449 filed January 8, 2003).

It was previously stated: "Savage teaches the making and use of a compound comprising one or more Class I MHC-peptide complexes an antibody or fragment thereof specific for a cell surface marker of a tumor cell (see entire document, Figure 1 in particular), including the elected species of CEA (paragraph bridging pages 5-6 in particular) or for cell surface marker on antigen presenting cells (see entire document, Figure 4 in particular. Savage teaches that the MHC molecule is linked to the carboxyl terminus of the antibody (see, for example, Figures 1 and 4 in particular).

Savage differs from the claimed invention in that the publication does not disclose class II MHC molecules or MelanA/MART (51-73) as an antigenic peptide bound to the MHC.

Cormier teaches that MelanA/MART-1 is a melanoma-associated antigen (MAA) that is present in a majority of melanomas (page 571, first column in particular). Cormier further teaches that tumor-infiltrating lymphocytes can recognize MelanA/MART-1 in the context of MHC class I presentation and can be detected in the peripheral blood of patients but "there have been few cases of objective tumor rejection" (page 571, first column in particular). Cormier also teaches that a possible explanation is that down-regulation of MAA by a tumor population provides a mechanism by which tumors escape immune recognition (page 571, second column in particular).

Schnell teaches that it is well established that T cell help can augment CTL function (Abstract in particular). Schnell further teaches that antigen presenting cells that present antigens in the context of both class I and class II stimulate a more robust cytotoxic response to the target tumor (see entire document).

The combination of references differs from the claimed invention in that they do not disclose MelanA/MART (51-73) as an antigenic peptide bound to class II MHC.

Zarour teaches that MelanA/MART (51-73) peptide was able to stimulate *in vitro* expansion of CD4+ T cells and specifically bound to MHC class II HLA-DR4 (see entire document). Zarour further teaches that CD4+ T cell reactivity against the MelanA/MART (51-73) peptide typically coexisted with a high frequency of anti- MelanA/MART (51-73) reactive CD8+ T cells in blood from HLA-A2+/DR4+ patients with melanoma (Abstract in particular).

It would have been prima facie obvious to a person having ordinary skill in the art at the time the invention was made to combine the teachings of the references. One would have been motivated with a reasonable expectation of success to create an MHC/antibody compound as taught by Savage to increase the presentation of antigenic peptides on the surface of the tumor cell. The artisan would have been further motivated to use a MelanA/MART antigenic peptide as the target because Cormier teaches that it is present in a majority of melanomas and because there may be down-regulation of MAA in tumor cells to escape immune recognition. The artisan would have been further motivated with a reasonable expectation of success to, based upon the teachings of Savage regarding the class I/antibody constructs, to also make class II/antibody constructs based upon the teachings of Schnell that T cell help (a class II driven event) augments the cytotoxic T cell response (a class I driven event) to tumors and the teachings of Zarour that no significant class I CD8+ T cell response were observed in patients in the absence of detectable class II CD4+ T cell response to MelanA/MART-1 (page 403, second column in particular).

Applicant's arguments filed January 21, 2004 have been fully considered but they are not persuasive. Applicant contends that that combination of references do not render the claimed invention obvious because Savage does not teach or suggest substituting MHC class I complexes (claimed) for MHC class II complexes (Savage) or linking the complex with a melanoma antigen to an antibody to a colon cancer surface marker.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Savage teaches an MHC class I molecule linked to an antibody specific for a tumor marker to target the MHC molecule to the cancer. Savage does not teach Applicant's antigen of interest, MelanA/MART-1. However, this antigen is taught by Cormier. Cormier also teaches tumors can be rejected by T cells recognizing this antigen but such rejection of tumors is rare, possibly due to down-regulation of expression of MelanA/MART-1 by the tumors in order to evade detection by those T cells. Accordingly, the artisan would recognize that boosting the antigenic presence on those cells would increase the likelihood of detection by the T cells. As correctly pointed out by Applicant, these teachings only specifically address MHC class I T cells. However, Schnell teaches that stimulating MHC class II helper T cells would enhance the MHC class I cytotoxic response because presenting antigens in the context of both MHC class I AND MHC class II results in an enhanced cytotoxic response to the antigen. Zarour teaches that the 51-73 peptide of MelanA/MART-1 can stimulate expansion of MHC class II-restricted helper T cells. The Court has staed that both the suggestion and the expectation of success must be **founded** in the prior art (emphasis added; *In re* Dow Chemical, 5 USPQ2d 1529 (Fed. Cir. 1988). The term "founded" refers to a foundation, meaning not only what is explicitly stated in the references, but also what would be in the knowledge base of the practitioner of the art. In the present case, the artisan would have recognized that the teachings of Savage could be used to increase the presence of antigen on tumor cells to overcome the protective mechanism taught by Cormier. Further, the artisan would have recognized from the teachings of Schnell that stimulation of helper T cells to react to the same cells as cytotoxic cells would enhance that cytotoxic response and would have recognized from the teachings of Zarour that the MelanA/MART-1 51-73 peptide can be used to stimulate helper T cells in the context of MHC class II. Applicant points out that the Court has said in *In re* Vaeck (20 USPQ2d 1438 (Fed. Cir. 1991)) that the teaching or suggestion to modify the prior art must come from the prior art itself, and not the application. The Examiner points out further that in the same decision the Court also said that the expectation of success in light of the prior art need only be a reasonable one and not absolute predictability. Given the level of skill attributable to the person of ordinary skill in the art at the time the invention was made, the artisan would have understood that engineering MHC class II molecules to bind to the same cancer cells as MHC class I and provide support for the cytotoxic response (Savage) would have provided a reasonable expectation that the normally low response to MelanA/MART-1 (Cormier), generating a more robust response (Schnell) to the same antigen (Zarour). References can be combined not only for what they individually suggest but also for what they, taken as a whole, would suggest to the person having ordinary skill in the art at the time the invention was made. See *In re* McLaughlin, 170 USPQ 209 (CCPA 1971).

Applicant's arguments filed July 28, 2004 have been fully considered but they are not persuasive.

Applicant quotes a passage from the remarks in the Final rejection mailed April 28, 2004 and asserts that this is not a proper motivation for combining the teachings of the cited references. Applicant should note, however, that the quoted passage was a portion of the further explanation of the original

rejection, which was maintained as originally applied. The explanation quoted by Applicant must be taken in the context of the original rejection, not as a stand-alone statement.

Applicant further argues that the references provide no motivation to combine an antibody to a colon tumor antigen (CEA) with a MHC class II molecule specific for a melanoma antigen (MelanA/MART (51-73) peptide). This position is not tenable because it is well known that CEA is not found exclusively on colon tumors, but is present on a wide range of tumors, including some metastatic melanomas. In the same regard, MelanA/MART is not the only tumor marker antigen expressed on melanomas but is the most commonly expressed as one of a milieu of antigens expressed by tumor cells. accordingly, it is not a matter of making a composition comprising an antibody to a colon tumor antigen and an MHC class II specific for a melanoma antigen, rather it is a matter of making a composition comprising an antibody to a widespread tumor antigen found on a plurality of tumors, including melanomas, and an MHC class II specific for an antigen found on most melanomas but may be down regulated, thus reducing its exposure to , MelanA/MART reactive T cells."

Applicant's arguments filed May 24, 2006 have been fully considered but they are not persuasive. Applicant argues that in the Advisory Action mailed April 14, 2006 the Examiner did not present a a factually supported *prima facie* conclusion of obviousness. Applicant asserts that the Examiner has attempted to improperly shift the burden to the Applicant by stating, "neither do the references provide any teaching that would suggest they could not be combined." The statement was taken out of context by Applicant as it was in response to Applicant's assertion in the arguments filed September 26, 2005 that there is no motivation *within* the references to combine the teachings. Furthermore, an Advisory Action is not the venue for presenting a *prima facie* conclusion of obviousness. As shown in the passages represented *supra* for Applicant's convenience, that *prima facie* conclusion of obviousness was presented in the original non-final Office Action mailed October 21, 2003 and supported in the final Office Actions mailed April 28, 2004 and March 24, 2005. Applicant continues to argue that there is no motivation to combine the references provided by the teachings and that the Examiner has used hindsight reasoning to construct the ground of rejection. However, the position is maintained that, as required, the motivation to combine the teachings is found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992) and that the references are properly combined not only for what they individually suggest but also for what they, taken as a whole, would suggest to the person having ordinary skill in the art at the time the invention was made. See *In re* McLaughlin, 170 USPQ 209 (CCPA 1971).

Conclusion

4. No claim is allowed.

5. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to F. Pierre VanderVegt whose telephone number is (571) 272-0852. The examiner can normally be reached on M-Th 6:30-4:00 and Alternate Fridays 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

F. Pierre VanderVegt, Ph.D.
Patent Examiner
August 14, 2006

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